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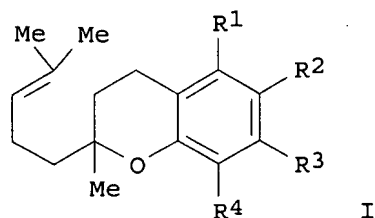
=> s cannabichromene
L1 428 CANNABICHROMENE

=> s mood(n)disorder
L2 30308 MOOD(N) DISORDER

=> s l1 and l2
L3 1 L1 AND L2

=> d ti au abs so py

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
TI Pharmaceutical compositions comprising cannabichromene-type
compounds for the treatment of mood disorders
IN Musty, Richard E.; Deyo, Richard
GI



AB The invention relates to the use of cannabichromene-type compds.
and derivs. thereof in the treatment of mood disorders
. Compds. of the invention include I (r1 = OH; R2 = H, COOH; R3 - C1-8
alkyl; R4 = H) and derivs. thereof.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PY 2005
2006
2006

=> s depression
L4 631079 DEPRESSION

=> s 11 and 14

L5 9 L1 AND L4

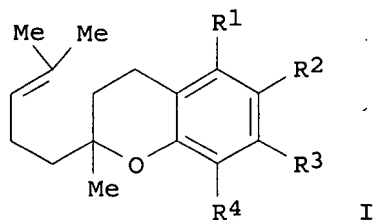
=> d ti au abs so py 1-9

L5 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

TI Pharmaceutical compositions comprising cannabichromene-type compounds for the treatment of mood disorders

IN Musty, Richard E.; Deyo, Richard

GI



AB The invention relates to the use of cannabichromene-type compds. and derivs. thereof in the treatment of mood disorders. Compds. of the invention include I (r1 = OH; R2 = H, COOH; R3 - C1-8 alkyl; R4 = H) and derivs. thereof.

SO PCT Int. Appl., 35 pp.

CODEN: PIXXD2

PY 2005

2006

2006

L5 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

TI Intraocular pressure, ocular toxicity and neurotoxicity after administration of Δ^9 -tetrahydrocannabinol or cannabichromene

AU Colasanti, Brenda K.; Powell, Stephen R.; Craig, Charles R.

AB Δ^9 -THC [1972-08-3] or cannabichromene [20675-51-8], a structurally diverse naturally occurring cannabinoid, was delivered unilaterally to the corneas of cats either acutely by application of single drops or chronically via osmotic minipumps over a period of 9 days. Whereas Δ^9 -THC only reduced intraocular pressure (IOP) minimally after acute administration, this cannabinoid produced substantial redns. in ocular tension during the entire period of chronic administration. Ocular toxicity during chronic treatment, however, was pronounced; conjunctival chemosis, erythema, and hyperemia were sustained, and corneal opacities approximating the site of drug delivery became evident within 3-5 days. In contrast, cannabichromene did not significantly alter IOP either acutely or during the 9 days of chronic administration, and ocular toxicity was not apparent. After systemic administration of Δ^9 -THC to rats, a dose-related increase in the appearance of 8-13 Hz polyspike discharges became evident in the electrocorticogram during wakefulness and behavioral depression. These polyspikes subsequently reappeared during rapid eye movement (REM) sleep episodes. Cannabichromene was devoid of this effect. It appears that, in contrast with acute administration, chronic delivery of Δ^9 -THC to cat eyes produces substantial redns. in IOP. The tension lowering effect, however, is accompanied by considerable ocular toxicity and neurotoxicity. As cannabichromene lacked these activities, the terpenoid portion of the cannabinoid structure appears to be important for their mediation.

SO Experimental Eye Research (1984), 38(1), 63-71

CODEN: EXERA6; ISSN: 0014-4835

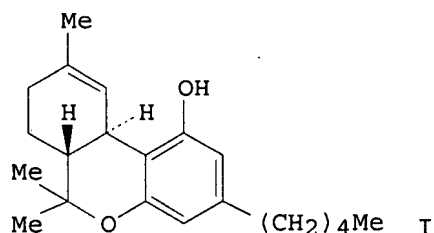
PY 1984

L5 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

TI The effect of cannabichromene on mean blood pressure, heart rate, and respiration rate responses to tetrahydrocannabinol in the anesthetized rat

AU O'Neil, J. D.; Dalton, W. S.; Forney, R. B.

GI



AB Expts. were conducted to investigate the potential for interaction of cannabichromene (CBC) [20675-51-8], a major cannabinoid present in cannabis, and Δ^9 -tetrahydrocannabinol (I) [1972-08-3], the primary active principle in cannabis. Male Wistar rats (220-260 g) were anesthetized with urethane and then given 2 mg/kg I, 10 mg/kg CBC, or bovine serum albumin vehicle according to a factorial (crossed) design. CBC had a hypotensive effect at the dose used in this study. CBC also caused a depression in respiration rate. When given alone, CBC had no effect on heart rate. The hypotensive effect and decreased respiration rate caused by I did not appear to be altered by simultaneous administration of CBC. CBC did, however, potentiate the decrease in heart rate caused by I. The mechanism of this interaction remains to be determined

SO Toxicology and Applied Pharmacology (1979), 49(2), 265-70

CODEN: TXAPA9; ISSN: 0041-008X

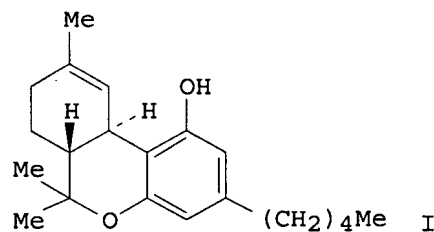
PY 1979

L5 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

TI Natural cannabinoids: apparent depression of nucleic acids and protein synthesis in cultured human lymphocytes

AU Nahas, G. G.; Desoize, B.; Armand, J. P.; Hsu, J.; Morishima, A.

GI



AB The lymphocyte response to phytohemagglutinin or to allogenic cells as measured by ^3H -thymidine incorporation was equally inhibited by 10^{-5} - 10^{-4} M of Δ^8 -tetrahydrocannabinol [5957-75-5] and Δ^9 -tetrahydrocannabinol (I) [1972-08-3], their 11-hydroxy metabolites, cannabidiol [13956-29-1], cannabinol [521-35-7], cannabichromene [20675-51-8], and cannabicyclol [21366-63-2]. A similar inhibiting effect on T lymphocyte transformation was also produced by a similar concentration of olivetol [500-66-3]. I depressed ^3H -leucine and ^3H -uridine uptake in cultured lymphocytes stimulated with phytohemagglutinin. Cannabinoids may

act directly on DNA formation by inhibition of precursor uptake and indirectly through inhibition of protein and RNA synthesis.

SO Pharmacol. Marihuana (1976), Volume 1, 177-86. Editor(s): Braude, Monique C.; Szara, Stephen. Publisher: Raven, New York, N. Y.

CODEN: 34AYA7

PY 1976

L5 ANSWER 5 OF 9 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Intraocular pressure, ocular toxicity and neurotoxicity after administration of $\Delta(9)$ -tetrahydrocannabinol or cannabichromene.

AU Colasanti B.K.; Powell S.R.; Craig C.R.

AB Δ -9-tetrahydrocannabinol ($\Delta(9)$ -THC) or cannabichromene, a structurally diverse naturally occurring cannabinoid, was delivered unilaterally to the corneas of cats either acutely by application of single drops or chronically via osmotic minipumps over a period of nine days. While $\Delta(9)$ -THC only reduced intraocular pressure (IOP) minimally after acute administration, this cannabinoid produced substantial reductions in ocular tension during the entire period of chronic administration. Ocular toxicity during chronic treatment, however, was pronounced; conjunctival chemosis, erythema, and hyperemia were sustained, and corneal opacities approximating the site of drug delivery became evident within three to five days. In contrast, cannabichromene did not significantly alter IOP either acutely or during the nine days of chronic administration, and ocular toxicity was not apparent. After systemic administration of $\Delta(9)$ -THC to rats, a dose-related increase in the appearance of 8-13 Hz polyspike discharges became evident in the electrocorticogram during wakefulness and behavioral depression. These polyspikes subsequently reappeared during rapid eye movement (REM) sleep episodes. Cannabichromene was devoid of this effect. These results indicate that, in contrast with acute administration, chronic delivery of $\Delta(9)$ -THC to cat eyes produces substantial reductions in IOP. The tension lowering effect, however, is accompanied by considerable ocular toxicity and neurotoxicity. As cannabichromene lacked these activities, the terpenoid portion of the cannabinoid structure appears to be important for their mediation.

SO Experimental Eye Research, (1984) Vol. 38, No. 1, pp. 63-71.

ISSN: 0014-4835 CODEN: EXERA6

PY 1984

L5 ANSWER 6 OF 9 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI The effect of cannabichromene on mean blood pressure, heart rate, and respiration rate responses to tetrahydrocannabinol in the anesthetized rat.

AU O'Neil J.D.; Dalton W.S.; Forney R.B.

AB Experiments were conducted to investigate the potential for interaction of cannabichromene (CBC), a major cannabinoid present in cannabis, and tetrahydrocannabinol (THC), the primary active principle in cannabis. Male Wistar rats (220-260 g) were anesthetized with urethane and then given 2 mg/kg THC, 10 mg/kg CBC, or bovine serum albumin vehicle according to a factorial (crossed) design. We demonstrated that CBC has a hypotensive effect at the dose used in this study. CBC also causes a depression in respiration rate. When given alone, CBC had no effect on heart rate. The hypotensive effect and decreased respiration rate caused by THC did not appear to be altered by simultaneous administration of CBC. CBC did, however, potentiate the decrease in heart rate caused by THC. The mechanism of this interaction is unknown.

SO Toxicology and Applied Pharmacology, (1979) Vol. 49, No. 2, pp. 265-270.

ISSN: 0041-008X CODEN: TXAPA9

PY 1979

L5 ANSWER 7 OF 9 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

TI INTRA OCULAR PRESSURE OCULAR TOXICITY AND NEURO TOXICITY AFTER
ADMINISTRATION OF DELTA-9 TETRA HYDRO CANNABINOL OR
CANNABICHROMENE.

AU COLASANTI B K [Reprint author]; POWELL S R; CRAIG C R
AB Δ -9-Tetrahydrocannabinol (Δ 9-THC) or cannabichromene
, a structurally diverse naturally occurring cannabinoid, was delivered
unilaterally to the corneas of cats either acutely by application of
single drops or chronically via osmotic minipumps over a period of nine
days. While Δ 9-THC only reduced intraocular pressure (IOP)
minimally after acute administration, this cannabinoid produced
substantial reductions in ocular tension during the entire period of
chronic administration. Ocular toxicity during chronic treatment was
pronounced; conjunctival chemosis, erythema, and hyperemia were sustained
and corneal opacities approximating the site of drug delivery became
evident within 3 to 5 days. Cannabichromene did not
significantly alter IOP either acutely or during the 9 days of chronic
administration, and ocular toxicity was not apparent. After systemic
administration of Δ 9-THC to rats, a dose-related increase in the
appearance of 8-13 Hz polyspike discharges became evident in the
electrocorticogram during wakefulness and behavioral depression.
These polyspikes subsequently reappeared during rapid eye movement (REM)
sleep episodes. Cannabichromene was devoid of this effect. In
contrast with acute administration, chronic delivery of Δ 9-THC to
cat eyes produces substantial reductions in IOP. The tension lowering
effect is accompanied by considerable ocular toxicity and neurotoxicity.
As cannabichromene lacked these activities, the terpenoid
portion of the cannabinoid structure appears to be important for their
mediation.

SO Experimental Eye Research, (1984) Vol. 38, No. 1, pp. 63-72.
CODEN: EXERA6. ISSN: 0014-4835.
PY 1984

L5 ANSWER 8 OF 9 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
TI THE EFFECT OF CANNABICHROMENE ON MEAN BLOOD PRESSURE HEART RATE
AND RESPIRATION RATE RESPONSES TO TETRA HYDRO CANNABINOL IN THE
ANESTHETIZED RAT.

AU O'NEIL J D [Reprint author]; DALTON W S; FORNEY R B
AB Experiments were conducted to investigate the potential for interaction of
cannabichromene (CBC), a major cannabinoid present in cannabis,
and tetrahydrocannabinol (THC), the primary active principle in cannabis.
Male Wistar rats (220-260 g) were anesthetized with urethane and then
given 2 mg/kg i.v. THC, 10 mg/kg CBC, or bovine serum albumin vehicle
according to a factorial (crossed) design. CBC has a hypotensive effect
at the dose used. CBC also causes a depression in respiration
rate. When given alone, CBC had no effect on heart rate. The hypotensive
effect and decreased respiration rate caused by THC did not appear to be
altered by simultaneous administration of CBC. CBC did potentiate the
decrease in heart rate caused by THC. The mechanism of this interaction
is unknown.

SO Toxicology and Applied Pharmacology, (1979) Vol. 49, No. 2, pp. 265-270.
CODEN: TXAPA9. ISSN: 0041-008X.
PY 1979

L5 ANSWER 9 OF 9 MEDLINE on STN
TI Intraocular pressure, ocular toxicity and neurotoxicity after
administration of delta 9-tetrahydrocannabinol or cannabichromene

AU Colasanti B K; Powell S R; Craig C R
AB delta-9-Tetrahydrocannabinol (delta 9-THC) or cannabichromene, a
structurally diverse naturally occurring cannabinoid, was delivered
unilaterally to the corneas of cats either acutely by application of
single drops or chronically via osmotic minipumps over a period of nine
days. While delta 9-THC only reduced intraocular pressure (IOP) minimally
after acute administration, this cannabinoid produced substantial

reductions in ocular tension during the entire period of chronic administration. Ocular toxicity during chronic treatment, however, was pronounced; conjunctival chemosis, erythema, and hyperemia were sustained, and corneal opacities approximating the site of drug delivery became evident within three to five days. In contrast, cannabichromene did not significantly alter IOP either acutely or during the nine days of chronic administration, and ocular toxicity was not apparent. After systemic administration of delta 9-THC to rats, a dose-related increase in the appearance of 8-13 Hz polyspike discharges became evident in the electrocorticogram during wakefulness and behavioral depression. These polyspikes subsequently reappeared during rapid eye movement (REM) sleep episodes. Cannabichromene was devoid of this effect. These results indicate that, in contrast with acute administration, chronic delivery of delta 9-THC to cat eyes produces substantial reductions in IOP. The tension lowering effect, however, is accompanied by considerable ocular toxicity and neurotoxicity. As cannabichromene lacked these activities, the terpenoid portion of the cannabinoid structure appears to be important for their mediation.

SO Experimental eye research, (1984 Jan) Vol. 38, No. 1, pp. 63-71.

Journal code: 0370707. ISSN: 0014-4835.

PY 1984

=> s bipolar
L6 134003 BIPOLAR

=> s l1 and l6
L7 1 L1 AND L6

=> s cannabinoid
L8 32364 CANNABINOID

=> d his

(FILE 'HOME' ENTERED AT 14:36:18 ON 09 NOV 2007)

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 14:36:35 ON 09 NOV 2007

L1 428 S CANNABICHROMENE
L2 30308 S MOOD(N)DISORDER
L3 1 S L1 AND L2
L4 631079 S DEPRESSION
L5 9 S L1 AND L4
L6 134003 S BIPOLAR
L7 1 S L1 AND L6
L8 32364 S CANNABINOID

=> s l8 and l2
L9 135 L8 AND L2

=> s l2(n)l8
L10 0 L2(N) L8

=> s l2(p)l8
L11 51 L2(P) L8

=> d ti au abs so py 1-10

L11 ANSWER 1 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of tetrahydro-pyrazolo[3,4-c]pyridine cannabinoid modulators
IN Xia, Mingde; Wachter, Michael; Pan, Meng; Liotta, Fina
GI For diagram(s), see printed CA Issue.
AB Title compds. I [location of double bonds in pyrazole ring depend on which of X2R2 or X1R1 is present or absent and only one can be present; X1, X2, X4-7 = absent or alkylene; X3 = absent, alkylene, alkylidene or NH; X7 is

absent when double bond present and R7 = (un)substituted CH-aryl or CH-heterocyclyl; R1 and R2 independently = H, (un)substituted alkyl, aryl, cycloalkyl, etc.; R4, R5, or R7 independently = H, halo, OH, etc.; R3 = COZ1R9, SO2NR10Z2R11 or CONR12Z3R13; R6 = H, aminoalkyl, alkylaminoalkyl, etc.; R7 = H, OH, halo, etc.; R9 and R11 independently = (un)substituted aryl, cycloalkyl or heterocyclyl; R10 = H or alkyl; R12 = H, alkyl or alkylcarbonyl; R13 = H, (un)substituted aryl, cycloalkyl, etc.; Z1 and Z2 = absent or alkyl; Z3 = absent, NH, SO2, or (un)substituted alkyl], and their pharmaceutically acceptable salts, are prepared and disclosed as cannabinoid modulators for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease. Thus, e.g., II was prepared by consecutive condensation reactions of 3-oxopiperidine-1-carboxylic acid tert-Bu ester with 4-fluorobenzaldehyde and oxalic acid di-Et ester followed by cyclocondensation with 2,4-dichlorophenylhydrazine, hydrolysis and amidation with 1-pyridin-2-ylethylamine. Cannabinoid receptor binding assays are described, e.g., II demonstrated an IC50 value of 13% in CB2 receptor binding inhibition assays.

SO PCT Int. Appl., 65pp.

CODEN: PIXXD2

PY 2007

2007

L11 ANSWER 2 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of tetrahydro-1h-1,2,6-triaza-azulene cannabinoid modulators

IN Xia, Mingde; Wachter, Michael; Pan, Meng

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [location of double bonds in pyrazole ring depend on which of X2R2 or X1R1 is present or absent and only one can be present; X1, X2, X4-8 = absent or alkylene; C3 = absent, alkylene, alkylidene or NH; X8 is absent when double bond present and R8 = (un)substituted CH-aryl or CH-heterocyclyl; R1 and R2 independently = H, (un)substituted alkyl, aryl, cycloalkyl, etc.; R4, R5, or R7 independently = H, halo, OH, etc.; R3 = COZ1R9, SO2NR10Z2R11 or CONR12Z3R13; R6 = H, aminoalkyl, alkylaminoalkyl, etc.; R8 = H, OH, halo, etc.; R9 and R11 independently = (un)substituted aryl, cycloalkyl or heterocyclyl; R10 = H or alkyl; R12 = H, alkyl or alkylcarbonyl; R13 = H, (un)substituted aryl, cycloalkyl, etc.; Z1 and Z2 = absent or alkyl; Z3 = absent, NH, SO2, or (un)substituted alkyl], and their pharmaceutically acceptable salts, are prepared and disclosed as cannabinoid modulators for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease. Thus, e.g., II was prepared by consecutive condensation reactions of 4-oxoazepane-1-carboxylic acid tert-Bu ester with 4-fluorobenzaldehyde and oxalic acid di-Et ester followed by cyclocondensation with 2,4-dichlorophenylhydrazine, hydrolysis and amidation with 1-aminopiperidine. Cannabinoid receptor binding assays are described, e.g., II demonstrated an IC50 value of 54% in CB1 receptor binding assays.

SO PCT Int. Appl., 70pp.

CODEN: PIXXD2

PY 2007

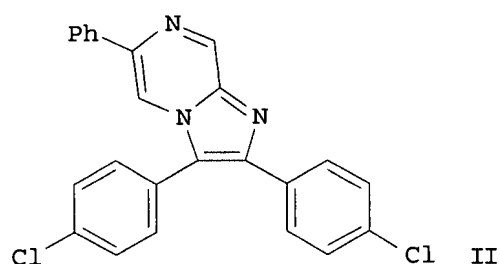
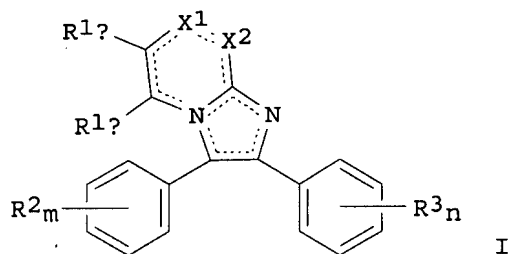
2007

L11 ANSWER 3 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of bicyclic heteroaryl derivatives as cannabinoid receptor modulators

IN Kundo, Mrinalkanti; Khairatkar-Joshi, Neelima; Nadkarni, Suhas M.; Pansare, Rameswar Madhavrao; Karnik, Pallavi V.

GI



AB Title compds. represented by the formula I [wherein X1 = CR, X2 = N or X1 = N, X2 = CR; R, R1a, R1b, R2, R3 = independently H, cyano, formyl, etc.; m = 1-5; n = 1-5; and analogs, N-oxides, tautomers, regioisomers, prodrugs, polymorphs, and pharmaceutically acceptable salts or solvates thereof] were prepared as cannabinoid receptor modulators. For example, reaction of (5-phenylpyrazin-2-yl)amine with 2-bromo-1-(4-chlorophenyl)-2-phenylethanone (preparation given) gave II. I were tested in in vitro for rat CB1 receptor binding using brain membrane and hCB1-CHO membranes, in vitro protocol for rat CB2 receptor binding using spleen membrane and hCB2-CHO membranes. Thus, I and their pharmaceutical compns. are useful for the treatment of diseases, conditions and/or disorders modulated by a cannabinoid receptor, such as pain, neurodegenerative disorders, eating disorders, weight loss or control, obesity, smoking cessation, alc. dependency, depression, and attention deficit hyperactivity disorder.

SO PCT Int. Appl., 172pp., which
CODEN: PIXXD2

PY 2007

L11 ANSWER 4 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of imidazo[1,2-a]pyridine cannabinoid receptor ligands for use as prodrugs in the treatment of CB1 and CB2 receptor disorders

IN Kundu, Mrinalkanti; Narayana, Lakshminarayana; Kotame, Prakash Murlidhar; Khairatkar-Joshi, Neelima; Karnik, Pallavi

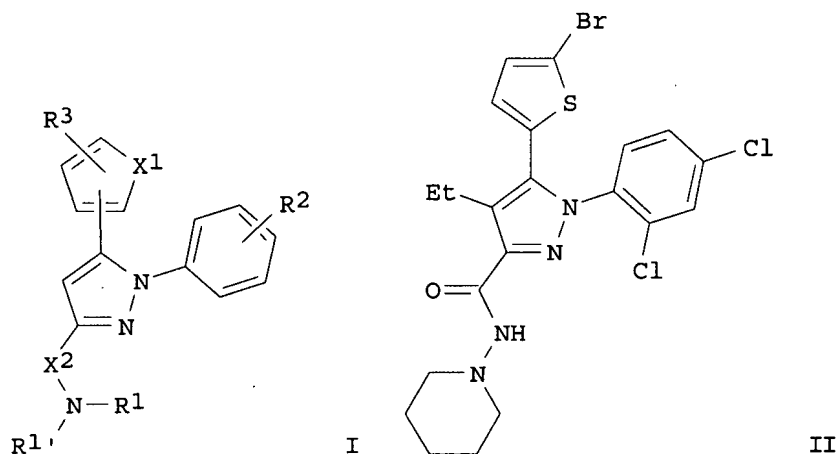
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to novel imidazo[1,2-a]pyridine cannabinoid receptor ligands, I and II wherein R1 is H, halo, nitro, cyano, alkyl; R2 and R3 are independently H, halo, nitro, cyano, or (un)substituted alkyl; R4 and R5 are independently H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted cycloalkyl etc. are prepared as cannabinoid receptor prodrugs. Thus, III was prepared and displayed an IC50 of 0.83 nM against human cannabinoid 2 receptors. I and II can be successfully employed cannabinoid 1 or cannabinoid 2 receptor ligands for treating diseases such as pain, neurodegenerative disorders, eating disorders, weight

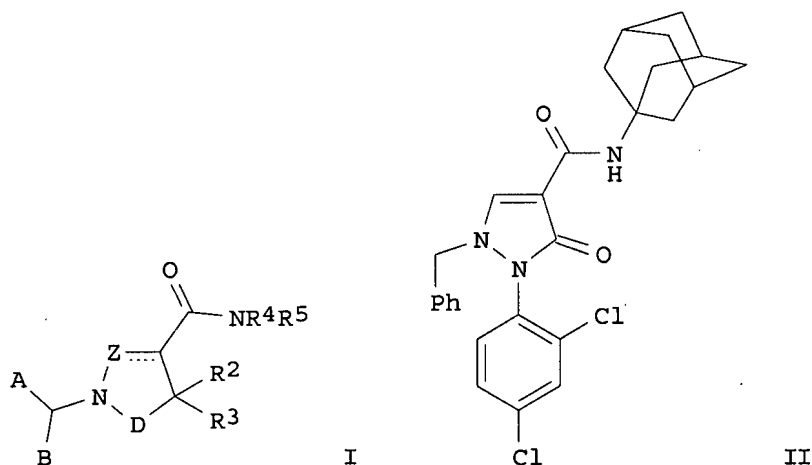
loss or control, obesity and diabetes.
SO PCT Int. Appl., 74pp.
CODEN: PIXXD2
PY 2007

L11 ANSWER 5 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Substituted 5-heteroaryl-1-phenyl-pyrazole cannabinoid modulators and
their preparation, pharmaceutical compositions and use in the treatment of
diseases
IN Xia, Mingde; Liotta, Fina; Pan, Meng; Wachter, Michael P.; Lu, Huajun
GI



AB This invention is directed to a substituted 5-heteroaryl-1-phenyl-pyrazole cannabinoid modulator compound of formula I: or a form thereof, and methods for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease. Compds. of formula I wherein X1 is O and S; X2 is carbonyl, alkenylcarbonyl and alkenylsulfoanyl; R1 is absent or H; R1' is (un)substituted C3-12 cycloalkyl, (un)substituted heterocyclyl, (un)substituted (hetero)aryl and (un)substituted alkyl; when R1 is absent R2 and R1' are taken together with the N to form (un)substituted heterocyclic ring; R2 is 1-4 substituents of (un)substituted alkyl, (un)substituted alkoxy, CN, halo, OH, amino, (un)substituted aminoalkyl, etc.; R3 is 1-2 substituents of (un)substituted alkoxy, CN, halo, OH, amino, and aminoalkyl; R4 is 1-3 substituents of (un)substituted alkyl, (un)substituted alkoxy, CN and halo; are claimed. Example compound II was prepared by acylation of 2-butanoyl-5-bromothiophene with di-Et oxalate; the resulting 3-[(5-bromothien-2-yl)carbonyl]-2-oxopentanoic acid Et ester underwent cyclization with 2,4-dichlorophenylhydrazine to give 5-(5-bromothien-2-yl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylic acid Et ester, which underwent hydrolysis to give the corresponding pyrazole-3-carboxylic acid, which underwent chlorination to give the corresponding acid chloride, which underwent amidation with 1-aminopiperidine to give compound II. All the invention compds. were evaluated for their cannabinoid modulatory activity. From the assay, it was determined that compound 29 % binding og CB2 at 0.2 μ M concentration
SO U.S. Pat. Appl. Publ., 39pp.
CODEN: USXXCO
PY 2007
2007
2007

L11 ANSWER 6 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN



AB The title compds. I [A, B = (un)substituted alkyl, aryl, heteroaryl, etc.; Z = C(O), CH₂, CH; D = O, NR₁; R₁ = H, (un)substituted alkyl, cycloalkyl, etc.; R₂, R₃ = H, alkyl; or R₂ and R₃ together with the carbon atom to which they are attached represent C(O); R₄, R₅ = H, (un)substituted alkyl, aryl, etc.; or NR₄R₅ = 3-7 membered (un)saturated cyclic ring which may optionally include at least two heteroatoms selected from O, S or (un)substituted NH], useful as cannabinoid receptor modulators, were prepared and formulated. E.g., a multi-step synthesis of II, starting from Et ethoxymethylenemalonate and 2,4-dichlorophenylhydrazine, was given. Exemplified compds. I were tested for CB₁ and CB₂ receptors binding (data given).

SO PCT Int. Appl., 177pp.

CODEN: PIXXD2

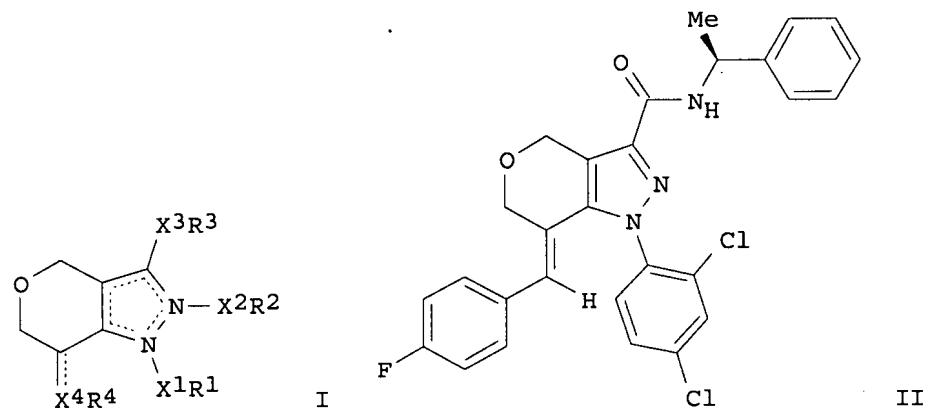
PY 2007

L11 ANSWER 8 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Tetrahydro-pyranopyrazole compounds displaying cannabinoid modulating activities and their preparation, pharmaceutical compositions and use in the treatment of CB receptor mediated diseases

IN Liotta, Fina; Lu, Huajun; Wachter, Michael P.

GI



AB This invention is directed to a tetrahydro-pyranopyrazole cannabinoid modulator compound of formula I: and a method for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease. Compds. of formula I wherein dotted lines in the ring is two double bond, and the remaining bonds are single bonds, and dotted line to X4R4 is an optional double bond; X1, X2 and X4 are independently absent and lower alkylene; X3 is absent, lower alkylene, lower alkylidene, and NH; R1, R2 and R4 are independently H, (un)substituted lower alkylene, lower alkylsulfonyl, (un)substituted aryl, (un)substituted C3-12cycloalkyl, and (un)substituted heterocyclyl; R3 is acyl, sulfonylamino, and carbonylamino; and their pharmaceutically acceptable salts, isomers, prodrugs, metabolites, and polymorphs thereof, are claimed. Example compound II was prepared by condensation of tetrahydropyran-4-one with 4-fluorobenzaldehyde; the resulting 3-(4-fluorobenzylidene)tetrahydropyran-4-one underwent acylation with oxalic acid di-Et ester to give 2-[5-(4-benzylidene)-4-oxotetrahydropyran-3-yl]-2-oxoacetic acid Et ester, which underwent cyclization with 2,4-dichlorophenylhydrazine to give the corresponding tetrahydropyranopyrazolecarboxylate, which underwent hydrolysis to give the corresponding tetrahydropyranopyrazole carboxylic acid, which underwent amidation with (R)-1-phenylethanol to give compound II. All the invention compds. were evaluated for their CB1 receptor binding affinity. From the assay, it was determined that compound II exhibited an IC50 valued of 0.013 μ M and 87 % binding.

SO PCT Int. Appl., 77pp.
CODEN: PIXXD2

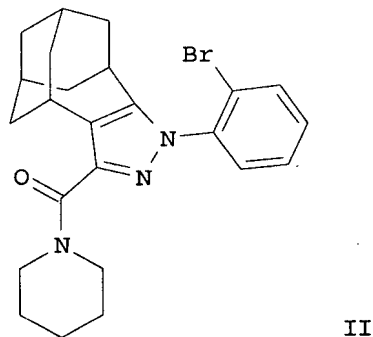
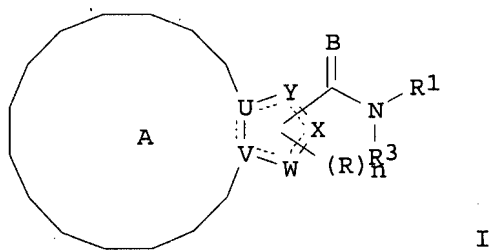
PY 2007
2007

L11 ANSWER 9 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Carboxamide derivatives as novel cannabinoid receptor ligands, pharmaceutical compositions containing them, and process for their preparation

IN Muthuppalaniappan, Meyyappan; Balasubramanian, Gopalan; Gullapalli, Srinivas; Joshi, Neelima Khairatkar; Narayanan, Shridhar

GI



AB The invention relates to carboxamide derivs. of formula I as cannabinoid receptor modulators, in particular cannabinoid 1 (CB1) or cannabinoid 2 (CB2) receptor modulators, and uses thereof for treating diseases, conditions and/or disorders modulated by a cannabinoid receptor (such as pain, neurodegenerative disorders, eating disorders, weight loss or control, and obesity). Compds. of formula I wherein dotted lines represents an optional double bond; U and V are independently C and N; W, X, and Y are independently C, N, O, C and CO with proviso that at least two on U, V, W, X and Y are N, O, CO and S; R, R1 and R2 are independently H, NO2, CN, formyl, acetyl, halo, OH and derivs., SH and derivs., oxo, thio, etc.; B is O, S, NH and derivs.; n is 0, 1, and 2; A is (un)substituted (hetero)tricycloalkyl, (un)substituted (hetero)tricycloalkenyl (un)substituted (hetero)bicycloalkyl, (un)substituted (hetero)bicycloalkenyl, etc.; and their analogs, pharmaceutically acceptable salts, esters, tautomers, regioisomers, stereoisomers, enantiomers, diastereoisomers, polymorphs, and solvates thereof are claimed. Example compound II was prepared by amidation of 5-(2-bromophenyl)-5,6-diazatetracyclo[7.3.1.1.3,11.04,8]tetradeca-4(8),6-diene-7-carboxylic acid with piperidine. All the invention compds. were evaluated for their cannabinoid receptor modulatory activity (data given).

SO PCT Int. Appl., 255pp.
CODEN: PIXXD2

PY 2006
2007

L11 ANSWER 10 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study

AU Scheen, Andre J.; Finer, Nick; Hollander, Priscilla; Jensen, Michael D.; Van Gaal, Luc F.

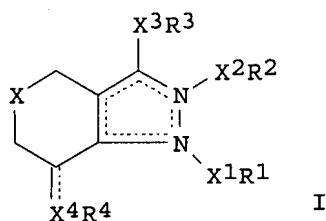
AB Background: Rimonabant, a selective cannabinoid type 1 receptor blocker, reduces bodyweight and improves cardiovascular and metabolic risk factors in non-diabetic overweight or obese patients. The aim of the RIO-Diabetes trial was to assess the efficacy and safety of rimonabant in overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulfonylureas. Methods: 1047 overweight or obese type 2 diabetes patients (body-mass index 27-40 kg/m²) with a Hb A1c (HbA1c) concentration of 6.5-10.0% (mean 7.3% [SD 0.9] at baseline) already on metformin or sulfonylurea monotherapy were given a mild hypocaloric diet and advice for increased phys. activity, and randomly assigned placebo (n=348), 5 mg/day rimonabant (360) or 20 mg/day rimonabant (339) for 1 yr. Two individuals in the 5 mg/day group did not receive double-blind treatment and were thus not included in the final anal. The primary endpoint was weight change from baseline after 1 yr of treatment. Analyses were done on an intention-to-treat basis. This trial is registered at, number . Findings: 692 patients completed the 1 yr follow-up; nos. in each group after 1 yr were much the same. Weight loss was significantly greater after 1 yr in both rimonabant groups than in the placebo group (placebo: -1.4 kg [SD 3.6]; 5 mg/day: -2.3 kg [4.2], p=0.01 vs placebo; 20 mg/day: -5.3 kg [5.2], p<0.0001 vs placebo). Rimonabant was generally well tolerated. The incidence of adverse events that led to discontinuation was slightly greater in the 20 mg/day rimonabant group, mainly due to depressed mood disorders, nausea, and dizziness. Interpretation: These data indicate that 20 mg/day rimonabant, in combination with diet and exercise, can produce a clin. meaningful reduction in bodyweight and improve HbA1c and a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes inadequately controlled by metformin or sulfonylureas.

SO Lancet (2006), 368(9548), 1660-1672
CODEN: LANCAO; ISSN: 0140-6736

PY 2006

=> d ti au abs so py 11-20

L11 ANSWER 11 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of tetrahydrothiopyrano[4,3-c]pyrazole as cannabinoid
modulators
IN Liotta, Fina; Lu, HuaJun; Xia, Mingde; Wachter, Michael P.
GI



AB The invention relates to a cannabinoid (CB) modulator compound (shown as I; variables defined below; e.g. (E)-2-(1-benzyl-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazol-3-yl)ethenesulfonic acid ((1R)-1-phenylethyl)amide (1)) or a pharmaceutically acceptable form thereof and a method for use in treating, ameliorating or preventing a CB receptor mediated syndrome, disorder or disease (no data). Although the methods of preparation are not claimed, prepns. and/or characterization data for 130 examples of I are included. For example, 1 was prepared in 6 steps starting with acylation of tetrahydro-4H-thiopyran-4-one by dimethoxyacetic acid Me ester and ending with coupling of 1-benzyl-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxaldehyde with (R)-PhCHMeN(Boc)SO₂Me. For I: the dashed lines between positions 2-3 and positions 3a-7a = the location for a double bond when X1R1 is present; the dashed lines between positions 3-3a and positions 7a-1 = the location for a double bond when X2R2 is present; the dashed line between position 7 and X4R4 = the location for a double bond. X is S, sulfoxo or sulfonyl; X1 is absent or is lower alkylene; X2 is absent or is lower alkylene; wherein only one of X1R1 and X2R2 are present; X3 is absent or is lower alkylene or lower alkylidene; when the dashed line between position 7 and X4R4 is absent, then X4 is absent or is lower alkylene; when the dashed line between position 7 and X4R4 is present, then X4 is absent. R1 is H or (un)substituted aryl, C3-C12 cycloalkyl, or heterocyclyl; R2 is H or (un)substituted aryl, C3-C12 cycloalkyl, or heterocyclyl; R3 is -C(O)heterocyclyl or -Z-N(R6)-Z1R7 ((un)substituted on heterocyclyl); when the dashed line between position 7 and X4R4 is absent, then R4 is H, hydroxy, lower alkyl, lower alkoxy, halogen, (un)substituted aryl; when the dashed line between position 7 and X4R4 is present, then R4 is CH-(un)substituted-aryl or CH-(un)substituted-heterocyclyl; R6 and R7 are each individually H, lower alkyl, -NR8R9, (un)substituted aryl, (un)substituted C3-C12 cycloalkyl or (un)substituted heterocyclyl; R8 and R9 are each individually H, alkyl, heterocyclyl, C3-C12 cycloalkyl, or (un)substituted aryl; Z is carbonyl or sulfonyl; Z1 is absent or is lower (un)substituted alkylene. Assay results for CB1 or CB2 agonist or inverse agonist activity are tabulated for 130 examples of I.

SO U.S. Pat. Appl. Publ., 74pp.
CODEN: USXXCO
PY 2006
2006

L11 ANSWER 12 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Beyond the cannabinoid receptors
AU Felder, Christian C.; Dickason-Chesterfield, Amy K.; Moore, Steven A.
AB A review. Cannabinoids, in the form of marijuana plant exts.,

have been used for thousands of years for a wide variety of medical conditions, ranging from general malaise and mood disorders to more specific ailments, such as pain, nausea, and muscle spasms. The discovery of tetrahydrocannabinol, the active principal in marijuana, and the identification and cloning of two cannabinoid receptors (i.e., CB1 and CB2) has subsequently led to biomedical appreciation for a family of endocannabinoid lipid transmitters. The biosynthesis and catabolism of the endocannabinoids and growing knowledge of their broad physiolo. roles are providing insight into potentially novel therapeutic targets. Compds. directed at one or more of these targets may allow for cannabinoid-based therapeutics with limited side effects and abuse liability.

SO Molecular Interventions (2006), 6(3), 149-161

CODEN: MIONAR; ISSN: 1534-0384

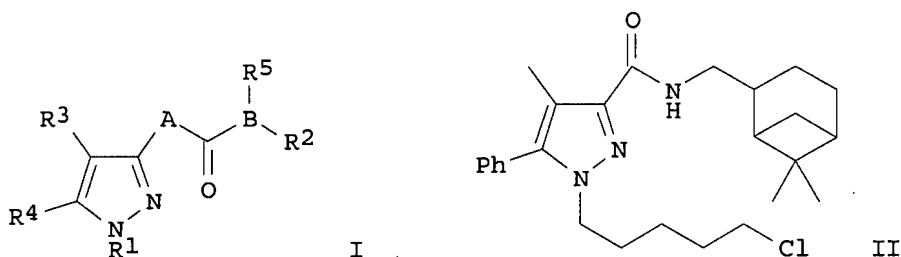
PY 2006

L11 ANSWER 13 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of arylpyrazolecarboxamides as CB1 cannabinoid receptor antagonists.

IN Makriyannis, Alexandros; Liu, Qian; Thotapally, Rajesh

GI



AB Title compds. [I; A = bond, O, (CH₂)₀₋₁NR₆; R₆ = H, alkyl; B = N, O; R₅ = null, H, (substituted) alkyl; R₁ = (substituted) carbon chain, (CH₂)_nZ; n = 0-7; Z = H, halo, N₃, NCS, cyano, NO₂, amino, etc.; R₂ = carbocyclyl, heterocyclyl, aryl, heteroaryl, naphthyl, tricyclyl, etc.; R₃ = H, halo, N₃, NCS, Ph, cyano, NO₂, amino, aroyl, OAc, SO₃H, etc.; R₄ = (CH₂)_nZ; Z = H halo, N₃, NCS, cyano, NO₂, amino, OAc, acyloxy, etc.], were prepared Thus, title compound (II) showed CB1 receptor affinity with IC₅₀ = 1.2 nM.

SO U.S. Pat. Appl. Publ., 46 pp., Cont.-in-part of U.S. Ser. No. 790,498.

CODEN: USXXCO

PY 2006

2001

2003

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2004

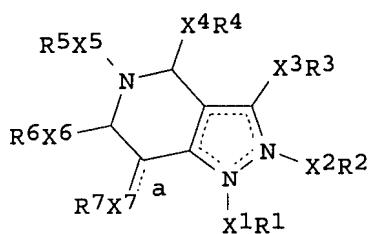
2004

L11 ANSWER 14 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

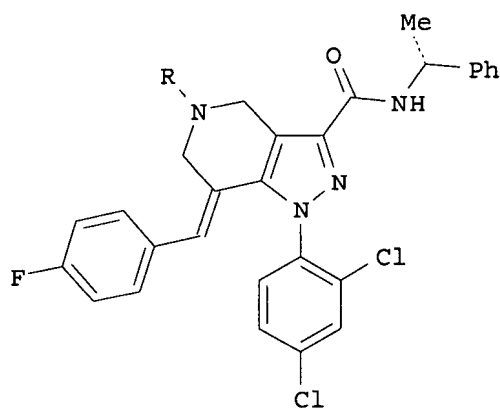
TI Preparation of tetrahydropyrazolopyridines as cannabinoid modulators

IN Xia, Mingde; Pan, Meng; Wachter, Michael P.; Liotta, Fina

GI



I



II

AB Title compds. I [wherein X1 - X6 = absent or alkylene; X3 = alkylidene or NH; R1, R2, R4, R5, R6 = H, (un)substituted alkyl, etc.; R3 = amido, ester, etc.; when a = single bond, X7 = absent or alkylene and R7 = H, OH, etc.; when a = double bond, X7 = absent and R7 = CH-aryl or CH-heterocyclyl] and salts, isomers, prodrugs, metabolites or polymorphs thereof were prepared as modulators of cannabinoid receptor CB1 and CB2. For instance, removal of Boc group II (R = Boc) with TFA (96% yield) followed by acylation with Me chloroformate (80% yield) gave II (R = C(O)OMe). In the binding assays, this product had IC50 of 0.003 μ M and 26% inhibition at a concentration of 0.2 μ M for cannabinoid receptor CB1 and CB2, resp. Other biol. data were also given. Therefore, I and their pharmaceutical compns. are useful in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease.

SO U.S. Pat. Appl. Publ., 71 pp.

CODEN: USXXCO

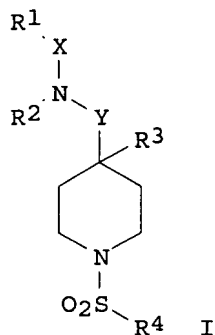
PY 2006
2006
2006
2006
2007
2007

L11 ANSWER 15 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of N-sulfonylpiperidine cannabinoid receptor 1 antagonists

IN Sher, Philip M.; Wu, Gang; Ewing, William R.

GI



I

AB The present invention describes N-sulfonylpiperidine compds. (I; R1 = alkyl, alkenyl, aryl, heteroaryl, arylalkyl, arylakenyl, alkoxy, aryloxy, arylalkoxy, alkylamino, dialkylamino, arylamino, arylalkylamino, heterocyclyl; R2 = substituted alkyl, substituted alkenyl, arylalkyl,

arylalkenyl, heteroarylalkyl; R3 = H, alkyl, alkenyl, arylalkenyl, OH, alkoxy, arylalkoxy; R4 = alkyl, alkenyl, aryl, heteroaryl, arylalkyl, arylalkenyl, alkylamino, arylamino, arylalkylamino, etc.; X = CO, SO2; Y = CR5R6, CR5R6CR7R8; R5-8 = H, alkyl, alkenyl, arylalkyl, arylalkenyl), including their prodrugs, pharmaceutically acceptable salts and stereomers, as CB1 receptor antagonists. Pharmaceutical compns. comprising at least one N-sulfonylpiperidine compound and optionally one or more addnl. therapeutic agents, and methods of treatment diseases or disorders associated with the activity of the CB1 receptor using the I compds. both alone and in combination with addnl. therapeutic agents are also described. The I compds. were useful for various therapeutic applications, such as for treatment of metabolic and eating disorders, cardiovascular diseases, nervous system and mental diseases, inflammatory disorders, cancer, substance abuse, autoimmune disorders, etc. Thus, the synthesis of various I compds. was provided.

SO U.S. Pat. Appl. Publ., 29 pp.

CODEN: USXXCO

PY 2006

2006

2006

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L11 ANSWER 16 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Discovery of a novel piperidinyl-sulfonyl benzoic ester, active as CB1 agonist

AU Lambeng, N.; Lebon, F.; Christophe, B.; Grossmann, M.; Burton, M.; De Ryck, M.; Quere, L.

AB The endocannabinoid system seems to be involved in a rising number of pathol. conditions. CNS responses to cannabinoids are mainly mediated by the G protein-coupled CB1 receptor, which is known to couple preferentially to Gi/Go G proteins. Due to its presynaptic distribution, and its coupling to various systems, CB1 receptor represents an ideal natural tool for modulating the neurotransmitter release. Therapeutic interest for searching CB1 agonists mainly lies in developing drugs for treating pain (chronic & acute), multiple sclerosis, tremor, anxiety/mood disorders, sleep disorders, seizures and for neuroprotection. Two products are already available on this growing (yet still controversial) market, namely Marinol and Nabilone as well as Sativex which is supposed to become available soon. In an effort to discover new CB1 agonists, we developed a high-throughput screening assay for identification of CB1 modulators using CHO-K1 cells stably expressing mitochondrially-targeted Aequorin, G(alpha)16 and the human CB1 receptor (Euroscreen). Validation of the HTS was performed with competition studies against [3H]CP 55,940 and GTPgammaS binding expts. One compound with an IC50 in the low nanomolar range was identified as a full agonist, and was further evaluated in secondary assays for selectivity and biol. activity. A preliminary SAR has been obtained around this potent agonist which can be used to further characterize this family of sulfonyl benzoic esters and further optimize in vivo pharmacol. profile and ADME properties.

SO Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006 (2006), MEDI-129 Publisher: American Chemical Society, Washington, D. C.

CODEN: 69HYEC

PY 2006

L11 ANSWER 17 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI A therapeutic role for cannabinoid CB1 receptor antagonists in major depressive disorders

AU Witkin, Jeffrey M.; Tzavara, Eleni T.; Davis, Richard J.; Li, Xia; Nomikos, George G.

AB A review. Cannabinoid receptors in the CNS have been implicated in the control of appetite, cognition, mood and drug dependence. Recent findings support the hypothesis that cannabinoid CB1 receptor

blockade might be associated with antidepressant and anti-stress effects. A novel potential antidepressant drug class based on this mechanism is supported by the neuroanatomical localization of CB1 receptors and signal transduction pathways that are involved in emotional responses, together with the antidepressant-like neurochem. and behavioral effects induced by CB1 receptor antagonists. Selective CB1 receptor antagonists are in development for the treatment of obesity and tobacco smoking, and could be tested for antidepressant efficacy because recent results of clin. studies suggest that they would also treat comorbid symptoms of depression such as cognitive deficiencies, weight gain, impulsivity and dependence disorders. Thus, CB1 receptor antagonism might constitute an integrated pharmacotherapeutic approach that impacts the affective, cognitive, appetitive and motivational neuronal networks involved in mood disorders.

SO Trends in Pharmacological Sciences (2005), 26(12), 609-617

CODEN: TPHSDY; ISSN: 0165-6147

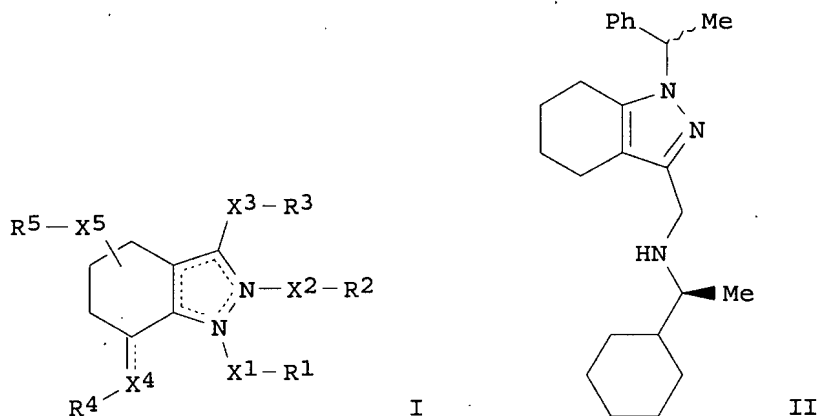
PY 2005

L11 ANSWER 18 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of tetrahydroindazole cannabinoid modulators

IN Lagu, Bharat; Liotta, Fina; Pan, Meng; Wachter, Michael P.; Xia, Mingde

GI



AB Title compds. I [X1-2 = absent, alkylene, wherein only one X1R1 and X2R2 are present; X3 = absent, alkylene, etc.; X4-5 = absent, alkylene; R1 = aryl, cycloalkyl, heterocyclyl, etc.; R2 = aryl, cycloalkyl, heterocyclyl, etc.; R3 = alkylcarbonyl, sulfonamido, etc.; R4 = CH-aryl, CH-heterocyclyl, etc.; R5 = H, OH, alkyl, alkoxy, etc.] are prepared For instance, II is prepared in 5 steps from 1-bromoethylbenzene, hydrazine, oxo(2-oxocyclohexyl)acetic acid (preparation given) and (S)-1-cyclohexylethylamine. II exhibits an IC50 = 0.05 for the CB1 receptor. I are useful in the treatment of a cannabinoid receptor mediated syndrome, disorder or disease.

SO PCT Int. Appl., 149 pp.

CODEN: PIXXD2

PY 2005

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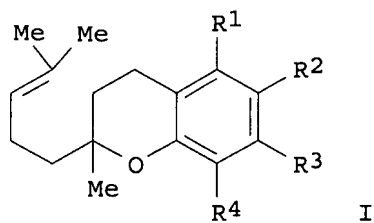
2007

2006

2007

L11 ANSWER 19 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Protein and cDNA sequences of novel human cannabinoid receptor interacting proteins and therapeutic use
IN Lewis, Deborah L.; Bhartur, Sheela; Wallis, Kathleen; Niehaus, Jason
AB The invention provides novel polypeptides capable of interacting with the CB1 cannabinoid receptor. Also provided are genomic and cDNA sequences encoding the CB1 receptor interacting proteins 1a and 1b (CRIPl a and CRIPl b) and antibodies to the CRIPl a and CRIPl b proteins. Also provided are methods of modulating the activity of the CB1 receptor and methods of screening for modulators of CRIPl a and CRIPl b activity on the CB1 receptor.
SO U.S. Pat. Appl. Publ., 77 pp.
CODEN: USXXCO
PY 2005

L11 ANSWER 20 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Pharmaceutical compositions comprising cannabichromene-type compounds for the treatment of mood disorders
IN Musty, Richard E.; Deyo, Richard
GI



AB The invention relates to the use of cannabichromene-type compds. and derivs. thereof in the treatment of mood disorders. Compds. of the invention include I (r1 = OH; R2 = H, COOH; R3 = C1-8 alkyl; R4 = H) and derivs. thereof.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PY 2005
2006
2006

=> d ti au abs so py 21-30

L11 ANSWER 21 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Upregulation of CB1 receptors and agonist-stimulated [35S]GTPyS binding in the prefrontal cortex of depressed suicide victims
AU Hungund, B. L.; Vinod, K. Y.; Kassir, S. A.; Basavarajappa, B. S.; Yalamanchili, R.; Cooper, T. B.; Mann, J. J.; Arango, V.
AB Endogenous and exogenous cannabinoids (CBs) acting through the CB1 receptors have been implicated in the regulation of several behavioral and neuroendocrine functions. Modulation of endocannabinoidergic system by ethanol in mouse brain, and the association of suicide and mood disorders with alcoholism suggest possible involvement of the cannabinoidergic system in the pathophysiol. of depression and suicide. Therefore, the present study was undertaken to examine the levels of CB1 receptors and mediated signaling in the dorsolateral prefrontal cortex (DLPFC) of subjects with major depression who had died by suicides (depressed suicides, DS). [3H]CP-55,940 and CB1 receptor-stimulated [35S]GTPyS binding sites were analyzed in membranes obtained from

DLPFC of DS (10) and matched normal controls (10). Upregulation (24%, $P < 0.0001$) of CB1 receptor d. (B_{max}) was observed in DS (644.6 ± 48.8 fmol/mg protein) compared with matched controls (493.3 ± 52.7 fmol/mg protein). However, there was no significant alteration in the affinity of receptor (DS; 1.14 ± 0.08 vs. control; 1.12 ± 0.10 nM). Higher d. of CB1 receptors in DS (38%, $P < 0.001$) was also demonstrated by Western blot anal. The CB1 receptor-stimulated $[35S]GTP\gamma S$ binding was significantly greater (45%, $P < 0.001$) in the DLPFC of DS compared with matched controls. The observed upregulation of CB1 receptors with concomitant increase in the CB1 receptor-mediated $[35S]GTP\gamma S$ binding suggests a role for enhanced cannabinoidergic signaling in the prefrontal cortex of DS. The cannabinoidergic system may be a novel therapeutic target in the treatment of depression and/or suicidal behavior.

SO Molecular Psychiatry (2004), 9(2), 184-190

CODEN: MOPSFQ; ISSN: 1359-4184

PY 2004

L11 ANSWER 22 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Marijuana addiction and CNS reward-related events

AU Gardner, Eliot L.

AB A review. The reward substrates of the central nervous system (CNS) consist of: (1) a core dopaminergic/enkephalinergic neural system synaptically interconnecting the ventral tegmental area, nucleus accumbens, and ventral pallidum, and which appears to mediate reinforcement; (2) a glutamatergic neural network originating in the frontal cortex and deep temporal lobe, which feeds into the core dopaminergic/enkephalinergic system and which appears to mediate aspects of reward-related incentive motivation; and (3) addnl. neural inputs - which use many different neurotransmitters, including 5-hydroxytryptamine (serotonin), GABA, and dynorphin - into the core dopaminergic/enkephalinergic system, which appear to regulate addnl. aspects of reward. These complex and interrelated systems are strongly implicated in drug addiction, and in such addiction-related phenomena as withdrawal dysphoria and craving. These systems are also implicated in the pleasures produced by such natural rewards as food and sex. On the basis of >15 yr of work, cannabinoids are now known to activate these CNS substrates and influence reward-related behaviors. From these actions, presumably, derive both the addictive potential of cannabinoids and possible clin. benefit in mood disorders such as depression.

SO Biology of Marijuana (2002), 75-109. Editor(s): Onaivi, Emmanuel S.

Publisher: Taylor & Francis Ltd., London, UK.

CODEN: 69CWLM; ISBN: 0-415-27348-X

PY 2002

L11 ANSWER 23 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Pharmacological actions and therapeutic uses of cannabis and cannabinoids

AU Kumar, R. N.; Chambers, W. A.; Pertwee, R. G.

AB This review highlights the pharmacol., pharmacokinetics, pharmacol. actions, therapeutic uses and adverse effects of cannabinoids. The effect of cannabinoids on anesthesia is mentioned briefly. Important advances have taken place in cannabinoid research over the last few years and have led to the discovery of novel ligands. The possible clin. applications of these ligands and the direction of future research are discussed.

SO Anaesthesia (2001), 56(11), 1059-1068

CODEN: ANASAB; ISSN: 0003-2409

PY 2001

L11 ANSWER 24 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Methods for the amelioration of neuropsychiatric disorders by inhibiting the inactivating transport of endogenous cannabinoid substances

IN Pionnelli, Daniele

AB The invention is directed to a method for ameliorating a neuropsychiatric disorder in a patient by inhibiting the inactivating transport of an

endogenous cannabinoid substance. The method comprises administration of a pharmaceutical composition able to inhibit the transport of an endogenous cannabinoid substance into cells. The administration is in an amount sufficient to inhibit the inactivating transport of an endogenous cannabinoid substance and to ameliorate the neuropsychiatric disorder in the patient.

SO PCT Int. Appl., 70 pp.

CODEN: PIXXD2

PY 2001

2002

L11 ANSWER 25 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Clinical trial experience with cannabinoids

AU Holdcroft, A.; Smith, M.; Smith, B.; Hodgson, H.; Evans, F. J.

AB The identification of a peripheral cannabinoid receptor localized to the immune system around the gastrointestinal tract stimulated a clin. trial of oral cannabinoids in a patient with chronic pain and inflammation of gastrointestinal origin. The patient had the symptoms of familial Mediterranean fever and required oral opioids for pain control before the study. A long-term randomized double-blind placebo-controlled study with capsules containing oil of cannabis (active) and virgin olive oil (placebo) demonstrated significant opioid sparing, with morphine used as escape analgesia, during three weeks of active treatment while pain scores remained similar in the three placebo weeks. There were no changes in inflammatory markers measured. Compliance was demonstrated by urine analyses for cannabinoids. Difficulties during this prolonged study were encountered with a lack of effectiveness during the final two weeks, which may have been induced by tolerance, and with mood disorders during two consecutive placebo weeks, which suggested withdrawal symptoms. Central effects during the active weeks were avoided by choosing a suitable dosage of tetrahydrocannabinol and with the marked reduction in morphine requirements achieved with the cannabinoid preparation. In future studies it should be possible to define the active constituents of the natural preparation and their appropriate route, which can produce these desirable analgesic effects.

SO Pharmaceutical Sciences (1997), 3(11), 546-550

CODEN: PHSCFB; ISSN: 1356-6881

PY 1997

L11 ANSWER 26 OF 51 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Endocannabinoids and their receptors as targets for treating metabolic and psychiatric disorders.

AU Felder C.C.

AB The CB1 receptor is arguably one of the most abundant GPCRs in the CNS and has long been attractive as a therapeutic target for a wide variety of therapeutic indications including pain, weight gain, emesis and mood disorders. Its cousin, the CB2 receptor, is highly localized in the immune cells regulating immune function and inflammatory pain. Direct acting nonselective agonists, while providing potentially broad therapeutic efficacy, also cause undesirable sedative and hypnotic side effects. New approaches to leverage cannabinoid biology for therapeutic benefit show promise of providing the therapeutic benefits without the buzz. .COPYRG. 2006 Elsevier Ltd. All rights reserved.

SO Drug Discovery Today: Therapeutic Strategies, (Jun 2006) Vol. 3, No. 4, pp. 561-567.

Refs: 38

ISSN: 1740-6773

PY 2006

L11 ANSWER 27 OF 51 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study.

AU Scheen A.J.; Finer N.; Hollander P.; Jensen M.D.; Van Gaal L.F.
AB Background: Rimonabant, a selective cannabinoid type 1 receptor blocker, reduces bodyweight and improves cardiovascular and metabolic risk factors in non-diabetic overweight or obese patients. The aim of the RIO-Diabetes trial was to assess the efficacy and safety of rimonabant in overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulphonylureas. Methods: 1047 overweight or obese type 2 diabetes patients (body-mass index 27-40 kg/m(2)) with a haemoglobin A(1c) (HbA(1c)) concentration of 6.0vrhdot.5-10.0vrhdot.0% (mean 7.0vrhdot.3% [SD 0.0vrhdot.9] at baseline) already on metformin or sulphonylurea monotherapy were given a mild hypocaloric diet and advice for increased physical activity, and randomly assigned placebo (n=348), 5 mg/day rimonabant (360) or 20 mg/day rimonabant (339) for 1 year. Two individuals in the 5 mg/day group did not receive double-blind treatment and were thus not included in the final analysis. The primary endpoint was weight change from baseline after 1 year of treatment. Analyses were done on an intention-to-treat basis. This trial is registered at ClinicalTrials.gov, number NCT00029848. Findings: 692 patients completed the 1 year follow-up; numbers in each group after 1 year were much the same. Weight loss was significantly greater after 1 year in both rimonabant groups than in the placebo group (placebo: -1.0vrhdot.4 kg [SD 3.0vrhdot.6]; 5 mg/day: -2.0vrhdot.3 kg [4.0vrhdot.2], p=0.0vrhdot.01 vs placebo; 20 mg/day: -5.0vrhdot.3 kg [5.0vrhdot.2], p<0.0vrhdot.0001 vs placebo). Rimonabant was generally well tolerated. The incidence of adverse events that led to discontinuation was slightly greater in the 20 mg/day rimonabant group, mainly due to depressed mood disorders, nausea, and dizziness. Interpretation: These data indicate that 20 mg/day rimonabant, in combination with diet and exercise, can produce a clinically meaningful reduction in bodyweight and improve HbA(1c) and a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes inadequately controlled by metformin or sulphonylureas. .COPYRGT. 2006 Elsevier Ltd. All rights reserved.

SO Lancet, (11 Nov 2006) Vol. 368, No. 9548, pp. 1660-1672.
Refs: 49
ISSN: 0140-6736 CODEN: LANCAO
PY 2006

L11 ANSWER 28 OF 51 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Comorbidity between substance use disorders and psychiatric conditions.
AU Schuckit M.A.
AB Aims: To review information relevant to the question of whether substance-induced mental disorders exist and their implications. Design and method: This paper utilized a systematic review of manuscripts published in the English language since approximately 1970 dealing with comorbid psychiatric and substance use disorders. Findings: The results of any specific study depended on the definitions of comorbidity, the methods of operationalizing diagnostic criteria, the interview and protocol invoked several additional methodological issues. The results generally support the conclusion that substance use mental disorders exist, especially regarding stimulant or cannabinoid-induced psychoses, substance-induced mood disorders, as well as substance-induced anxiety conditions. Conclusions: The material reviewed indicates that induced disorders are prevalent enough to contribute significantly to rates of comorbidity between substance use disorders and psychiatric conditions, and that their recognition has important treatment implications. The current literature review underscores the heterogeneous nature of comorbidity. .COPYRGT. 2006 American Psychiatric Association.

SO Addiction, (Sep 2006) Vol. 101, No. SUPPL. 1, pp. 76-88.
Refs: 138
ISSN: 0965-2140 E-ISSN: 1360-0443 CODEN: ADICE5
PY 2006

L11 ANSWER 29 OF 51 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Cannabis use and mood disorders: Patterns of clinical presentations among adolescents in a developing country.

AU Konings M.; Maharajh H.D.

AB Notwithstanding the increase use of cannabis among adolescents in both developing and developed countries, few studies have looked at cannabis use and mood disorders. In a series of case studies, this research project seeks to investigate patterns of clinical presentations seen among cannabis users in psychiatric outpatients in Trinidad. Five clinical patterns of presentations are identified among cannabis users and abusers based on variables of dosing, age of initial use, duration of use, tolerance and reverse tolerance and poly-drug abuse. All patients in these case studies were standardized for method of use and potency of cannabis used. Patients were screened by urine tests to determine co-morbid use of other substances. Other variables such as environmental factors and genetic vulnerability were reviewed as far as possible from historical accounts of family members. The five patterns described are low, controlled use with mild euphoria and heightened awareness, moderate use with mixed depressive symptoms and suicidal behaviour, heavy, short term use with manic symptoms, long term incremental use with psychotic symptoms due to the trumping of depressive symptoms and cannabis mixed with other substances resulting in florid psychosis. Mood disorders appear to be a common finding among adolescents using cannabis. Sensitization to symptomatic presentation and early detection of cannabis use in young adolescents are necessary. Further research is needed on the effect of cannabinoids on emotions, behaviour and thinking and its relationship to mental disorders. This study is useful as a guideline for the implementation of public health strategies and legislation concerning the use of cannabis in youths. .COPYRGHT. Freund Publishing House Ltd.

SO International Journal of Adolescent Medicine and Health, (Apr 2006) Vol. 18, No. 2, pp. 221-233.

Refs: 32

ISSN: 0334-0139 CODEN: IJAHE8

PY 2006

L11 ANSWER 30 OF 51 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Cannabinoid biology: The search for new therapeutic targets.

AU Felder C.C.; Dickason-Chesterfield A.K.; Moore S.A.

AB Cannabinoids, in the form of marijuana plant extracts, have been used for thousands of years for a wide variety of medical conditions, ranging from general malaise and mood disorders to more specific ailments, such as pain, nausea, and muscle spasms. The discovery of tetrahydrocannabinol, the active principal in marijuana, and the identification and cloning of two cannabinoid receptors (i.e., CB(1) and CB(2)) has subsequently led to biomedical appreciation for a family of endocannabinoid lipid transmitters. The biosynthesis and catabolism of the endocannabinoids and growing knowledge of their broad physiological roles are providing insight into potentially novel therapeutic targets. Compounds directed at one or more of these targets may allow for cannabinoid-based therapeutics with limited side effects and abuse liability.

SO Molecular Interventions, (1 Jun 2006) Vol. 6, No. 3, pp. 149-161.

Refs: 141

ISSN: 1534-0384 CODEN: MIONAR

PY 2006

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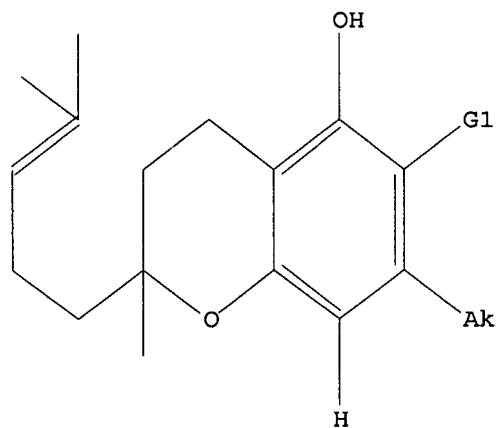
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FULL SCREEN SEARCH COMPLETED - 3197 TO ITERATE

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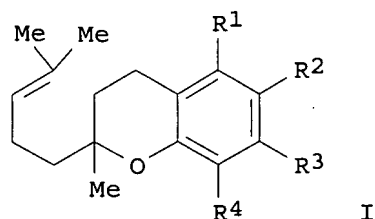
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L4 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Pharmaceutical compositions comprising cannabichromene-type compounds for the treatment of mood disorders

IN Musty, Richard E.; Deyo, Richard

GI



AB The invention relates to the use of cannabichromene-type compds. and derivs. thereof in the treatment of mood disorders. Compds. of the invention include I (r1 = OH; R2 = H, COOH; R3 - C1-8 alkyl; R4 = H) and derivs. thereof.

SO PCT Int. Appl., 35 pp.

CODEN: PIXXD2

PY 2005

2006

2006

L4 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Methods for the synthesis of 5'-alkyl resorcinol and cannabinoid derivatives and uses as contraceptive formulations

IN Travis, Craig R.

AB The present invention provides a method of contraception involving applying at least one 5'-alkyl resorcinol and/or cannabinoid (e.g., cannabinol derivative (including, but not limited to, tetrahydrocannabinols), cannabidiol derivative, cannabigerol derivative, etc.) to an individual in an amount

and at a location sufficient to prevent pregnancy. The invention also provides formulations particularly useful as a barrier contraceptive comprising at least one 5'-alkyl resorcinol and/or cannabinoid.

SO PCT Int. Appl., 46 pp.

CODEN: PIXXD2

PY 2004

2004

2004

L4 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Topical formulations of resorcinols and cannabinoids and methods of use

IN Travis, Craig R.

AB The invention provides a method for preventing the transmission of HIV from one individual to another. In accordance with the method, a pharmacol. acceptable composition including at least one resorcinol derivative and/or cannabinoid (e.g., cannabinol derivs., Δ^8 -THC derivs., cannabichromene derivs., cannabidiol derivs., cannabigerol derivs.) (including combinations thereof) is administered topically to a first

individual harboring HIV, or to a second individual at risk of infection with HIV, proximate in time with contact between the first individual and the second individual. The invention also provides topical formulations of at least one resorcinol and/or cannabinoid and water insol. polymers as hydrogels.

SO PCT Int. Appl., 68 pp.

CODEN: PIXXD2

PY 2003

2003

2003

2005

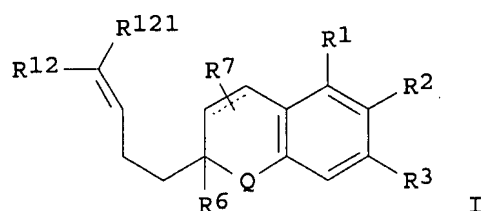
2006

L4 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of cannabichromenes as antivirals

IN Travis, Craig R.

GI



AB Title compds. [I; R1 = H, alkyl, CO₂H, OH, (substituted) alkoxy, alkanoyl, morpholinoalkylcarbonyloxy, etc.; R2 = H, OH, CO₂H, halo, alkoxy, etc.; R3 = (substituted) alkyl, haloalkyl, CO₂H, alkenyl, alkynyl, etc.; R6 = H, OH, halo, alkoxy, alkylthio, alkyl, haloalkyl, cyano, N₃, CO₂H, etc.; R7 = H, OH, halo, alkoxy, alkylthio, alkyl, haloalkyl, cyano, N₃, CO₂H, alkoxy, carbonyl, O, S, etc.; R12, R121 = H, OH, halo, alkoxy, alkylthio, alkyl, haloalkyl, cyano, N₃, CO₂H, alkoxy, carbonyl, etc.; R12R121 = O, S; Q = O, S, NW; W = H, alkoxy, carbonyl, alkyl, haloalkyl, alkoxy, haloalkyl, etc.], were prepared. Thus, 1-(1,1,5-trimethylhexyl)-3,4,5-trimethoxybenzene (preparation given), geraniol, and TsOH were refluxed 2 h in PhMe to give 20% 3,4-dihydro-2-methyl-2-(4-methyl-3-pentenyl)-7-(1,1,5-trimethylhexyl)-2H-1-benzopyran-5-ol (IG-08). IG-08 inhibited HIV-1 attachment and fusion to HeLa CD4 cells with suppression of μ -galactosidase activity.

SO PCT Int. Appl., 39 pp.

CODEN: PIXXD2

PY 2002

2002

2002

2002

2003

2003

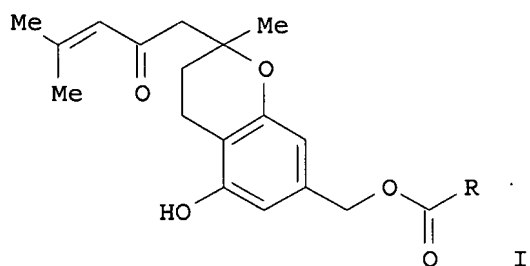
2004

L4 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of chroman derivatives as NGF induction agents

IN Arimoto, Yasushi; Hirano, Takaaki; Inakuma, Takahiro

GI



AB Chroman derivs. of formula I [R = alkyl, alkenyl] are prepared as nerve growth factor (NGF) induction agents. Thus, I (R = pentadecyl) was prepared from Me 3,5-dihydroxybenzoate, palmitic acid, Me vinyl ketone and di-Me 2-oxo-4-methyl-3-pentenylphosphonate. With I (R = pentadecyl) at 0.14 µg/mL the NGF d. in the cultured cell was 1.9 times the control.

SO Jpn. Kokai Tokkyo Koho, 9 pp.

CODEN: JKXXAF

PY 1999

L4 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Boron trifluoride etherate on alumina - a modified Lewis acid reagent(V) a convenient single-step synthesis of cannabinoids

AU Baek, Seung-Hwa; Yook, Chan Nam; Han, Du Seok

AB A simple and convenient method for intra- and intermol. Friedel-Crafts alkylation in the presence of boron trifluoride-etherate and basic alumina in methylene chloride is reported. Thus, alkylation of 5-alkylresorcinols with terpenoid alcs. gave cannabinoid derivs. In the above reactions, subsequent intramol. cyclizations were not observed, due to the mildness of the BF₃-di-Et ether on alumina reagent, which catalyzes the Friedel-Crafts reaction bt apparently does not attack olefins to form cationic centers.

SO Bulletin of the Korean Chemical Society (1995), 16(3), 293-6

CODEN: BKCSDE; ISSN: 0253-2964

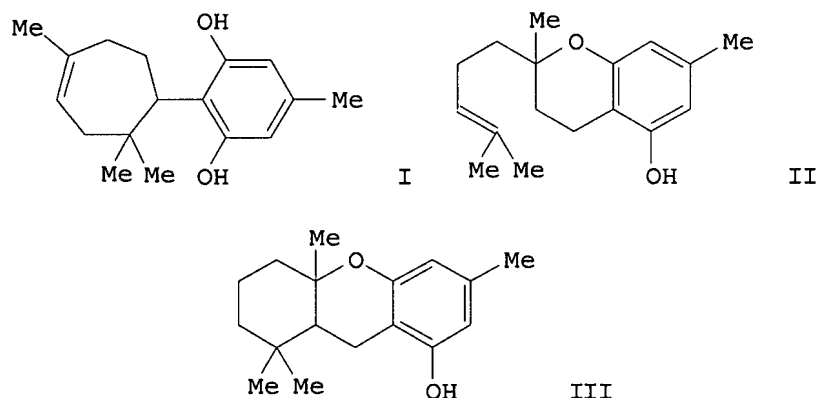
PY 1995

L4 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Alkylation of orcinol with nerol with modified Lewis acid.

AU Yook, Chan-Nam; Baek, Seung-Hwa; Cho, Sung-Dong; Park, No-Yeun

GI



AB Alkylation of, orcinol, 3,5-(HO)2C6H3Me, with nerol gave 33% cycloheptene I (BF₃.OEt₂-CH₂Cl₂-Imin-alumina-reflux), or 42% benzopyran II (BF₃.OEt₂-CH₂Cl₂-Imin-reflux), or 40% dibenzopyran III

(BF₃.OEt₂-CH₂Cl₂-alumina-3 h., room temperature).

SO Bulletin of the Korean Chemical Society (1992), 13(5), 457-8
CODEN: BKCSDE; ISSN: 0253-2964

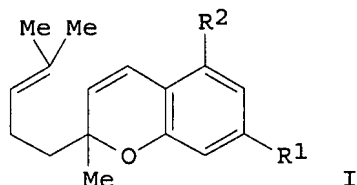
PY 1992

L4 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Cannabichromenes as antiinflammatory, hypothermic and antimicrobial drugs

IN Elsohly, Mahmoud; Turner, Carlton E.; Murphy, James C.; Wirth, Phillip W.

GI



AB The title compds. I (R₁, R₂ = H, alkyl, alkenyl, OH) and their di- and tetrahydro derivs. are useful for inducing hypothermia, reducing inflammation, and as antimicrobial agents. I.p. injection of 2-methyl-2-(4-methylpent-3-enyl)-5-hydroxy-7-methylchroman (480 mg/kg) totally suppressed the carrageenan-induced rat paw edema.

SO U.S., 8 pp. Cont.-in-part of U.S. Ser. No. 136,554, abandoned.
CODEN: USXXAM

PY 1989
1982

L4 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds

AU Elsohly, Hala N.; Turner, Carlton E.; Clark, Alice M.; Elsohly, Mahmoud A.

AB Cannabichromene homologs, analogs, and isomers as well as the C₁-homolog and isomer of cannabigerol were prepared and tested for their antibacterial and antifungal properties.

SO Journal of Pharmaceutical Sciences (1982), 71(12), 1319-23
CODEN: JPMSAE; ISSN: 0022-3549

PY 1982

L4 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Biogenetic-type synthesis of isoprenoid and diisoprenoid derivatives of orcinol

AU Manners, G.; Jurd, L.; Stevens, K.

AB The products formed by condensation of orcinol with 2-methyl-3-buten-2-ol, with geraniol, and with linalool in aqueous solns. of organic acids were separated and identified. C-isoprenyl- and C-geranyl orcinols are obtained as major products. Minor amts. of the hydrates, chromans, chroman hydrates, and hexahydroxanthene derivs. are also formed.

SO Tetrahedron (1972), 28(11), 2949-59
CODEN: TETRAB; ISSN: 0040-4020

PY 1972

L4 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Isolation and structure of Δ⁺- tetrahydrocannabinol and other neutral cannabinoids from hashish

AU Gaoni, Yechiel; Mechoulam, Raphael

AB The isolation and elucidation of the structures of Δ¹-tetrahydrocannabinol (Δ¹-THC), cannabigerol, cannabichromene, andcannabicyclol are described. A facile conversion of cannabidiol into Δ¹-THC takes place on treatment with BF₃.Et₂O. The absolute configuration of the chiral

centers at C-3 and C-4 of Δ^1 -THC is established as R.
SO Journal of the American Chemical Society (1971), 93(1), 217-24
CODEN: JACSAT; ISSN: 0002-7863
PY 1971

L4 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
TI Stereoselective cyclizations of cannabinoid 1,5-dienes
AU Mechoulam, Raphael; Yagen, B.
GI For diagram(s), see printed CA Issue.
AB Trans-Cannabigerol (I), m. 49-50°, identical with the natural product, was prepared in 52% yield by condensation of geraniol and olivetol in CH_2Cl_2 in the presence of p-MeC₆H₄-SO₃H. Cis-Cannabigerol (II) (dinitrobenzoate m. 76°) was prepared in 39% yield from nerol and olivetol. I (250 mg) in 0.2 ml H₂SO₄ treated with 16 ml MeNO₂ 15 min at -30° gave 88% III, 3% IV, and 5% V. Under similar conditions II gave 71% IV, 8.1% III, and 20.7% V. The results contrasted with those obtained for the acid-catalyzed cyclizations of trans- and cis-demethylfarnesic esters, which both gave the same trans product (Stadler, P.A., et al. 1957). The stereospecific cyclization was initiated by direct proton addition to the terminal double bond.
SO Tetrahedron Letters (1969), (60), 5349-52
CODEN: TELEAY; ISSN: 0040-4039
PY 1969

L4 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
TI Phosphate esters. I. The synthesis of phenolic isoprenoids from allylic phosphates
AU Miller, J. A.; Wood, H. C. S.
AB The synthesis of a series of allyl diphenyl phosphates is described. Reaction of these phosphate esters with a variety of phenols was studied. The products are usually coumarans or chromans, and the method was used for the synthesis of phenolic natural products containing isoprenoid residues. In particular, the reaction of 2,3,5-trimethylquinol with phytyl diphenyl phosphate gave α -tocopherol in excellent yield. These expts. establish that allylic phosphate esters can function as efficient alkylating agents in chemical systems. They also simulate the role played by pyrophosphate esters in biol. systems and demonstrate the chemical feasibility of biogenetic hypotheses which were suggested. 33 references.
SO Journal of the Chemical Society [Section] C: Organic (1968), (14), 1837-43
CODEN: JSOAX; ISSN: 0022-4952
PY 1968

L4 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
TI Chroman derivatives
GI For diagram(s), see printed CA Issue.
AB The title compds. (I) are prepared by reaction of divalent phenols (II) with reactive phosphates or sulfonates of alcs. (III). Thus, a mixture of 2.2 g. hydroquinone and 6.4 g. IV (R = R₄ = Me) (IVa) was heated in a silver-lined vessel 18 hrs. at 100°. The dark colored mixture in 50 ml. Et₂O, after washing with aqueous NaHCO₃, was extracted with 5N NaOH. The extract was acidified and extracted again with Et₂O and worked up by usual methods to give 2 g. of an oily residue, which was chromatographed through a column of Al₂O₃ using AcOEt as eluant. The dark red oil was purified by recrystn. from petroleum ether and sublimation at 0.1 mm. to yield 0.6 g. 2,2-dimethyl-6-hydroxychroman, m. 74.5-5°. Similarly, the following I (R = Me) were prepared (R₄, substituents in positions 5, 6, 7, 8, and m.p. given): Me, Me, OH, Me, Me (Ia), 94.5-5.0°; Me₂C:CHCH₂CH₂, Me, OH, Me, Me, -; Me[CHMe(CH₂)₃]₃, Me, OH, Me, Me, -. The preparation of Ia from V (R = R₄ = Me) (Va) and from VI (R = R₄ = Me) (VIa) by similar methods is also given. Heating 1.31 g. orcinol hydrate and 4.1 g. farnesyl diphenyl phosphate 12 hrs. at 80° gave a dark red oil which in Et₂O was extracted with N NaHCO₃, 2N NaOH, and H₂O. The residue was

chromatographed through an Al₂O₃ column to give 3 fractions using as eluants: (a) petroleum ether, yielding 2.16 g. (44%) of a dichroman derivative (structure not given); (b) Et₂O in C₆H₆ (increasing from 50 to 100%), giving 0.7 g. of a slightly colored product, which was rechromatographed (eluant Et₂O-C₆H₆ 1:9) to give 18% 2,7-dimethyl-2-(4,8-dimethylnona-3,7-dienyl)-5-hydroxychroman; (c) AcOEt in Et₂O (increasing from 50 to 100%), giving 1.20 g. of an oil, which after addnl. chromatography over Al₂O₃ (eluant Et₂O-C₆H₆ 1:1) gave 23% 2,5-dimethyl-2-(4,8-dimethylnona-3,7-dienyl)-7-hydroxychroman. The preparation of most of the starting materials is also given. Thus, 24 ml. (PhO)₂P(O)Cl was added dropwise over 1 hr. at 0° to a solution of 86 g. allyl alc. (IIIa) in 16 ml. dry, freshly distilled C₅H₅N. After stirring the mixture 2 hrs. at this temperature it was divided between H₂O and Et₂O. The organic solution was washed successively

with

N H₂SO₄, aqueous NaHCO₃, and H₂O, dried and evaporated to give 70% IVa as an almost colorless viscous oil. Starting resp. from geraniol (0.1 mole) and phytol (0.1 mole) the following IV were prepared similarly (R, R₄ and yield given): Me, Me₂C:CHCH₂CH₂, 21.2 g.; Me, Me[CHMe(CH₂)₃]₂, 4.75 g. Va was prepared thus: 6.5 ml. C₅H₅N was added dropwise over 1.5 hrs. at 0° to a mixture of 3.44 g. IIIa and 7.8 g. p-toluenesulfonyl chloride. After stirring the mixture 0.5 hr. it was taken up in Et₂O and washed successively with 2N HCl, 2N NaOH, and H₂O to give 32% Va as a colorless oil. Finally, 7.2 g. (4-O₂NC₆H₄O)₂P(O)Cl (m. 96-7°; preparation given) was added to a mixture of 1.72 g. IIIa in Et₂O during which an exothermic reaction occurred. At 0°, 1.2 ml. C₅H₅N was added over 0.5 hr. to yield, after the usual work-up, 16% VI as a viscous, pale yellow oil.

SO 10 pp.

PY 1965

L4 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

TI Model experiments in the biosynthesis of phenolic isoprenoids

AU Miller, J. A.; Wood, H. C. S.

AB Allylic phosphate esters function as efficient alkylating agents in chemical systems. They also simulate the role played by pyrophosphate esters in biol. systems. Ten products produced from interactions of phenols and allyl or 3,3-dimethylallyl phosphate esters were analogous to compds. which occur naturally. These products were identified by spectroscopic methods or by microanalysis.

SO Chemical Communications (London) (1965), (3), 39-40

CODEN: CCOMA8; ISSN: 0009-241X

PY 1965

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